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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2005 and 18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 11/1/2005, in which claims 86, 87, 108 and 118 were amended. Claims 86-118 are pending in the instant application and are under consideration.

Any rejection of record in the previous office action not addressed herein is withdrawn. This action is not final due to new grounds of rejection that are made herein that were not necessitated by applicants' amendment of the claims in the response filed on 11/1/2005.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claim 106 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The *E. coli* strain deposited at the CNCM under the No. I-2025 does not contain a mutation in an aminoacyl-tRNA synthetase gene. Therefore the claim fails to further limit claim 103, which requires the isolated cell to have at least one mutation in an aminoacyl-tRNA gene as compared with the sequence of the corresponding wild-type gene. **This is a new objection.**

Claims 116-118 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or

rewrite the claim(s) in independent form. The claims are depend from the process of claim 108, wherein the unconventional amino acid contains an R group that is a radical containing a functional group, such as an aldehyde, ketone, ethenyl, enthynyl, or nitrile group. The claims encompass the use of amino acids containing functional groups that are capable of reacting easily and specifically with a chemical or biochemical compound under conditions which make it possible not to modify the activity of the protein or which avoid modifying the conventional amino acids. Claim 108 depends from claim 86, which requires that the unconventional amino acid the "that encoded by said target codon" (i.e. the codon prior to mutation). Thus, the only amino acids encompassed by the independent claim are those conventional amino acids incorporated into proteins of organisms such as bacteria or yeast. The amino acids encompassed by dependent claims 116 and 117 are broader in scope than the naturally occurring amino acids. **This is a new objection.**

Claim Rejections - 35 USC § 112

Claims 86-118 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for providing bacterial cells or yeast cells with the capacity to produce a protein, the amino acid sequence of which comprises at least one unconventional amino acid, does not reasonably provide enablement for the use of any other cell type such as a mammalian cell or insect cell in the claimed method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The nature of the invention is complex, involving the use of selection pressures to select cells comprising a mutation that allow the cell to incorporate unconventional amino acids. The claimed methods utilize a missense mutation in a gene encoding an essential protein for a target cell to select for cells that acquire the ability to compensate for the loss of the function of the essential protein. The method encompasses the steps of (a) introducing at least one missense mutation in a target codon of a gene encoding a protein required for the growth of the cells, and (b) selecting the cells obtained in (a) in a culture medium which (1) does not contain a nutrient compensating for the loss of functionality of the mutated protein and (2) contains the amino acid encoded by the target codon. Thus, the method selects for mutations that compensate for the loss of function of the gene containing the missense mutation.

The claimed method is capable of providing bacterial cells capable of inserting a conventional amino acid at codons that normally provide for the insertion of the amino acid and a codon (i.e. the one specified by the missense mutation) that does not normally provide for the insertion of the amino acid. The specification defines "unconventional amino acid" broadly to encompass conventional amino acids that are incorporated in place of the amino acid which

should normally be incorporated at this site with regard to the translated sequence (e.g. page 2, lines 31-39).

Breadth of the claims: The claims are broad in that cells isolated from any organism may be used in the method. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions using bacterial cells, such as *E. coli*, yeast cells, insect cells as well as animal cells, in particular mammalian cells such as Chinese hamster ovary (CHO) cells (e.g. page 6, lines 16-24). The specification describes experiments where *E. coli* cells modified to include missense mutations in an essential gene are grown in defined media (e.g. minimal media) in the presence of large quantities of an amino acid encoded by the original target codon of the essential protein (i.e. prior to the incorporation of the missense mutation), where the selective media does not comprise a nutrient whose requirement is necessitated by the missense mutation of the essential protein. The working examples are solely directed to embodiments where selective pressure is applied by culturing in defined media 1) lacking a nutrient required by the mutation of the essential protein, and 2) in the presence of the amino acid encoded by the target codon prior to its alteration to a missense codon. In each of the working examples, applicants were able to demonstrate a mutation in the aminoacyl-tRNA synthetase corresponding to the missense codon which allows the mutated aminoacyl-tRNA synthetase to incorporate amino acids other than the one specified by the missense codon (e.g. the amino acid encoded by the original target codon or other, non-canonical amino acids such as aminobutyrate). The specification teaches two working examples wherein the mutated aminoacyl-tRNA synthetase obtained via their selection methods

apparently has increased ability to incorporate non-canonical amino acids such as L-2-aminobutyrate or L-3-thiol-2-aminobutyrate (e.g. Examples 6-7).

The specification does not provide specific teachings or working examples directed to the use of insect cells or mammalian cells in the claimed method.

Predictability and state of the art: At the time the invention was made, the state of the art with regard to screening for bacterial cells or yeast cells comprising missense suppressors was well-developed (e.g. Murgola et al, Journal of Bacteriology, Vol. 143, No. 1, pages 285-292, 1980; Chiu et al, Genetics, Vol. 145, pages 707-714, 1997; Seale et al. Genetics, Vol. 86, pages 261-274, 1977). In contrast, the use of cells such as mammalian cells or insect cells was underdeveloped at the time the invention was made. For example, Drabkin et al (Molecular and Cellular Biology, Vol. 18, No. 3, pages 1459-1466, 1998) teach the sequence modification of a human initiator tRNA and provide the first example of missense suppression in mammalian cells (e.g. Abstract). Therefore, at the time the invention was made either no missense suppressor screens had been performed in mammalian cells or the screens had been performed unsuccessfully. Thus, it would be unpredictable for one to practice the claimed invention in cells other than bacterial or yeast cells.

Amount of experimentation necessary: The quantity of experimentation is high, as the skilled artisan could not rely on the teachings of the instant specification or prior art to adapt the claimed method to the use of cells other than bacterial or yeast cells. In order to carry out the claimed invention, one would first need to select a cell type, such as a CHO cell, and a gene essential for the growth of said cell. Next, one would have to introduce a missense mutation into the gene. One would then need to develop a culture medium lacking the nutrient compensating

for the loss of function. One could then develop the screening process for that cell type and missense mutation. This would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 86-118 are not considered to be fully enabled by the instant specification.

Claims 103-105 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **The grounds of this rejection have been changed in response to Applicants' amendment of the claims in the response filed on 11/1/2005.**

The rejected claims are drawn to host cells obtained by methods of selection wherein a missense mutation is incorporated into a an essential gene (required for growth of the host cell) at a target codon and the cell is grown under selective conditions wherein 1) the culture medium does not contain a nutrient that will compensate for the lack of a functional copy of the essential gene product, and 2) the culture medium contains an amino acid encoded by the target codon (prior to mutation). Further, the cell must comprise an aminoacyl-tRNA synthetase which recognizes a given amino acid and which is capable of charging onto one of its associated tRNAs

an unconventional amino acid or an amino acid other than said given amino acid, wherein the gene encoding the aminoacyl-tRNA synthetase contains at least one mutation compared with the sequence of the corresponding wild-type gene. The rejected claims thus comprise a set of cells isolated from any organism that encompass a mutation in an aminoacyl-tRNA synthetase gene, which is capable of mischarging a tRNA in the cell and suppressing a missense mutation in an essential gene.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes *E. coli* strains deposited at the CNCM under the Nos. I-2025, I-2026, I-2027, I-2339, I-2340, and I-2341, also referred to as strains β5366, β8144, β8146, β5479, β5485, and β5486, respectively (e.g. pages 7-9). Strain I-2025 (β5366) does not meet the structural or functional limitations of the claims in that the strain is incapable of growing without thymine or thymidine due to the absence of a mutation in any gene capable of suppressing the missense mutation in the thyA gene (e.g. Example 1). Strains I-2026 and I-2027 contain the K277Q allele of the ValS gene (e.g. page 24, lines 23-25). Strain I-2339 contains the R223H allele of the ValS gene (e.g. page 8, lines 13-24). Strain I-2340 contains the V276A allele of the ValS gene (e.g. page 8, lines 25-34). Strain I-2341 contains the D230N allele of the ValS gene (e.g. page 9, lines 7-8). Thus, each of the strains described in the instant specification is a strain of *E. coli* with a missense mutation in the ValS gene. The specification does not describe mutations in any other *E. coli* aminoacyl-tRNA synthetase genes. The

specification does not describe any mutations in an aminoacyl-tRNA synthetase gene of a cell isolated from any other type of organism, either prokaryotic or eukaryotic. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of *E. coli* strains with missense mutations in the ValS gene. The results are not necessarily predictive of other mutations that will confer the claimed function. Thus, it is impossible for one to extrapolate from the few examples described herein those isolated cells that would necessarily meet the structural/functional characteristics of the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the genetic modifications required to confer the claimed function, and therefore conception is not achieved until reduction to practice has occurred; regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound

itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Given the very large genus of isolated cells encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to genetic modifications of aminoacyl-tRNA synthetase that meet the functional limitations of the claims, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of isolated cells. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 103-105 and 107.

Response to Arguments/112 1st Rejection

Applicant's arguments filed 7/18/2005 have been fully considered but they are not persuasive. The response asserts that claim 103 does not encompass any mutant of any gene that will compensate for the loss of the essential gene product. Further, the response asserts that the compensation for the loss of the essential gene product is due to the mutation occurring in the tRNA synthetase gene, as is described in the instant specification with respect to strains β5366, β8144, β8146, β5479, β5485, and β5486. This is not found persuasive because the specification only describes strains of *E. coli* with a missense mutation in the ValS gene (β8144, β8146,

β5479, β5485, and β5486). The specification does not describe mutations in any other *E. coli* aminoacyl-tRNA synthetase genes. The specification does not describe any mutations in the aminoacyl-tRNA synthetase genes of a cell isolated from any other type of organism, either prokaryotic or eukaryotic. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
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